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# Clinical Manifestations and Management of Neurofibromatosis Type 1

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**Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with variable expression. The complications are age specific. Neurologic complications include tumors of the peripheral nerves, nerve roots, and plexi; spinal cord compression; dural ectasias; learning disabilities; attention deficit; headaches; seizures; brain tumors; deafness; hydrocephalus; and stroke. High-intensity signals on brain magnetic resonance imaging are a frequent finding without known clinical significance. Most brain tumors are benign and asymptomatic, but malignant brain tumors occur. The major cause of death is malignancy, including brain tumors and malignant peripheral nerve sheath tumors. Management includes genetic counseling, regular eye examinations, and careful physical exams.**


**KEYWORDS** neurofibromatosis type 1, NF1, neurofibromas, learning disabilities, peripheral nerve tumors, brain tumors

Although both the central and peripheral forms of neurofibromatosis (NF) were recognized in the 19th century, for many years neurofibromatosis was discussed as a single entity. Not until 1980 were patients with bilateral vestibular schwannomas (acoustic neuroma) and multiple central nervous system tumors recognized to have a distinct genetic disease, neurofibromatosis type 2 (NF2).[1] The condition characterized by von Recklinghausen with multiple café-au-lait spots, cutaneous neurofibromas, plexiform neurofibromas, and bony abnormalities is neurofibromatosis type 1 (NF1).[2]

## Diagnostic Criteria for NF1

NF1 is an autosomal dominant disorder with an incidence of 1 in 3,500 live births. Half of all cases are spontaneous mutations. Although recent advances in genetic testing may permit the laboratory diagnosis in as many as 95%, for the majority of patients, the diagnosis is made on the basis of clinical manifestations. Diagnosis requires the presence of 2 or more major criteria: 6 or more café au lait spots, axillary or inguinal freckling, 2 or more cutaneous neurofibromas, 1 plexiform neurofibroma, characteristic bony lesions (pseudarthrosis, sphenoid wing hypoplasia), an optic glioma, 2 or more iris Lisch nodules, or a first-degree relative with NF1[3] (Table 1). In some, the diagnosis can be made at birth, whereas others must be observed for a few years for the presence of additional criteria.

## Variability of Expression and Age-Specific Complications

NF1 is an extraordinarily variable condition. Some patients have very mild manifestations, whereas others are severely affected.[4] Complications such as café-au-lait spots and cutaneous neurofibromas occur in at least 95% of patients, whereas other features occur in less than 1%. There is no consistency in manifestations within a pedigree. NF1 is a progressive condition; different complications occur at specific times and some complications worsen over time. Café-au-lait spots, pseudarthrosis, and externally visible plexiform neurofibromas are apparent within the first year of life. Freckling, optic gliomas, and severe scoliosis occur by 7 years of age. Cutaneous neurofibromas and iris Lisch nodules tend to appear in teenage or young adult years. Malignancy, pheochromocytomas, and paraspinal plexiform neurofibromas are mostly problems of adults.

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**Table 1** Diagnostic Criteria for NF1

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|---|
| 6 or more café-au-lait spots, ≥0.5 cm in prepubertal children >1.5 cm in postpubertal individuals |
| Axillary or inguinal freckling |
| 2 or more cutaneous neurofibromas |
| 1 plexiform neurofibroma |
| 2 or more iris Lisch nodules |
| An optic glioma |
| A characteristic bony lesion (pseudarthrosis, hypoplasia of sphenoid wing, severe kyphoscoliosis) |
| First degree relative with NF1 |

In order to make the diagnosis, at least 2 major criteria are required.

## Cutaneous Manifestations of NF1

Café-au-lait spots are generally the heralding feature of NF1. Café-au-lait spots are hyperpigmented flat spots that are oval or rounded with fairly smooth borders (Fig 1) They must be at least 0.5 cm in diameter in prepubertal individuals and 1.5 cm in postpubertal patients. They are present at birth in many individuals and increase in size and number over the first 5 to 7 years of life. Most, but not all patients with NF1 have café-au-lait spots. There is no evidence that 1 large area of hyperpigmentation equals multiple café-au-lait spots. Large areas of hyperpigmentation occur in NF1 but also in normal individuals. Diffuse freckling is common in NF1, but hyperpigmentation (of any size) in the axilla or groin is very unusual except in NF. Freckling may not appear until 5 to 7 years of age.

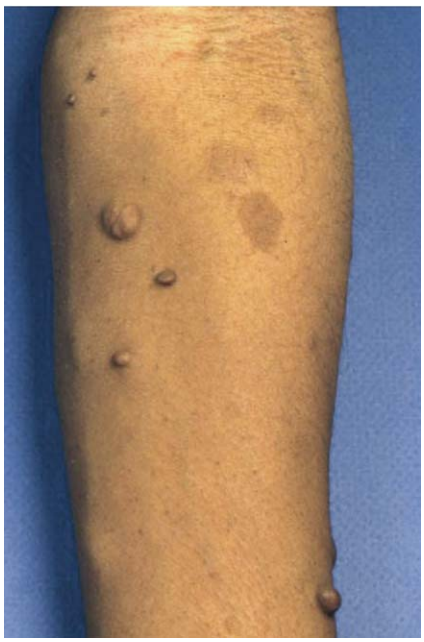

**Figure 1** Café-au-lait spot and pedunculated cutaneous neurofibromas. This adult has at least 6 raised, soft, well-circumscribed, pedunculated neurofibromas. Cutaneous neurofibromas may first appear as purplish flat, even depressible lesions. The patient also has a prominent rounded macule, which is a café-au-lait spot.

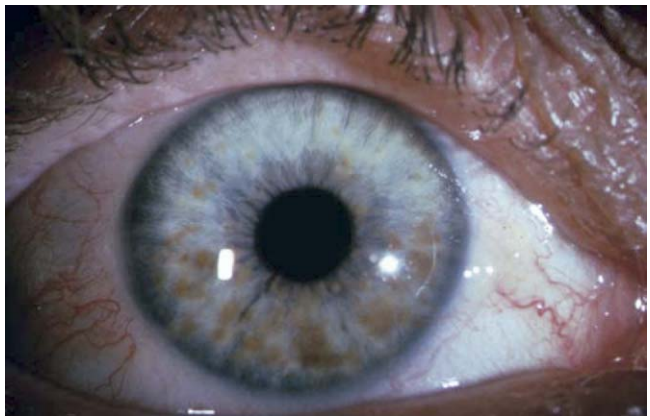

**Figure 2** Lisch nodules. This adult has multiple reddish brown spots in the lower pole of the iris that are slightly raised proliferations of melanocytes and fibroblasts. In brown-eyed individuals, Lisch nodules manifest as pale, hypopigmented spots in the iris. Lisch nodules are uncommon before age 10 years.

Cutaneous or dermal neurofibromas are tumors of the nerve sheath comprised of Schwann cells, fibroblasts, perineural cells, mast cells, axons, and blood vessels.[5] They may appear in childhood but more commonly develop in teenagers or adults (Fig 1). They may be purplish depressions in the skin or pedunculated lesions. Plexiform neurofibromas are histologically similar to cutaneous neurofibromas but have more extracellular matrix. They often arise from the dorsal spinal roots, nerve plexi, large nerve trunks, or sympathetic chains. Plexiform tumors may be discrete, homogeneous, and well circumscribed or diffuse, heterogeneous, and infiltrative. They may involve superficial skin or be entirely internal. They occur in at least 50% of patients and are probably present at birth. Many are asymptomatic.[6] The extent and timing of growth of plexiform tumors is unpredictable (Fig 3). Diffuse neurofibromas involve the epidermis and dermis extending up to the fascia, often forming a cap-like lesion of the scalp.[7] They seem to be confined to the scalp and stop growing in puberty. Schwannomas occur in NF1 but are primarily a feature of NF type 2 (NF2).

## Ocular/Orbital Manifestations of NF1

NF1 may affect the iris, retina, optic nerve, and the bony and soft tissue of the orbit. Lisch nodules are proliferations of melanocytes and fibroblasts that appear as reddish brown spots in the iris of blue- or green-eyed people and hypopigmented spots in brown eyed people. They are commonly found in the lower pole of the iris and have no affect on vision (Fig 2). Onset is usually in the teenage years. They are present in 90% of adults. Retinal hamartomas occur in a small percent of patients. Optic gliomas (visual pathway tumors) are grade I pilocytic astrocytomas found in 15% of patients. They produce thickening of the optic nerve. Frequently bilateral and often involving the chiasm, they may extend to the optic tracts or inferiorly into the hypothalamus.[8] They may present

as decreased color vision or an afferent papillary defect and later with pallor of the optic disc or a decrease in visual acuity between 15 months to 7 years of age.[9]

Congenital ptosis is a common finding in NF1 and may be bilateral or unilateral. It is not predictive of orbital pathology. However, orbital asymmetry is indicative of some degree of hypoplasia of the greater wing of the sphenoid. In its most severe form, this appears to be a progressive resorption of the sphenoid wing causing proptosis.[10] Plexiform neurofibromas of the orbit are frequently found in patients with optic gliomas.

## Orthopedic Problems

The most common orthopedic problems are hypotonia and poor coordination. Bony dysplasia, bony erosion, demineralization, nonossifying fibromas, and scoliosis are all features of NF1. Dysplastic bony lesions include splayed ribs, vertebral anomalies, hypoplasia of the sphenoid or mandible, and pseudarthrosis.[11] Pseudarthrosis occurs in 3% of patients and usually involves the distal one third of the tibia and fibula. The radius and ulna are less commonly affected. It presents at birth or within the first months of life as bowing of the affected extremity. Plain radiographs reveal pencil-point tapering of the tibia and/or fibula with anterior lateral bowing. Fracture is frequent, and surgical correction is difficult.[12] The fractures do not readily heal, hence the name pseudarthrosis or false joint. Prophylactic bracing should be instituted as soon as the lesion is recognized, before weight bearing, and continued to skeletal maturity.

Erosion or demineralization of bones is often caused by pressure from adjacent plexiform neurofibromas or the proliferation of blood vessels associated with some tumors. Nonossifying fibromas occur mainly in late childhood or early teenage years and can lead to fracture. The most common sites are the femur, tibia, and humerus. Nonossifying fibromas are often painful, and surgical treatment is problematic. Intervention should be limited to supportive measures and treatment of fractures.

Scoliosis occurs in at least 10% of patients; there are multiple forms.[13,14] There is a severe rapidly progressive kyphoscoliosis between 3 to 5 years of age that requires surgical correction. Idiopathic juvenile scoliosis occurs in teenage years and is often self-limited and treated with bracing. Scoliosis can also occur because of vertebral instability secondary to vertebral erosion or vertebral dysplasia. Vertebral erosion is caused by adjacent plexiform neurofibromas or less commonly dural ectasias.

## Short Stature and Hormonal Problems

Abnormalities in growth are a common feature of NF1. Large head size is present in half of patients and is not associated with any intracranial or endocrinologic pathology. Short stature is also common and is not usually associated with hormonal dysfunction. Failure to gain weight occurs in less than 1% of patients in the first 2 to 3 years of life. Precocious puberty and hypothalamic dysfunction occurs in some patients with visual pathway tumors. Gynecomastia is a rare complication of prepubertal boys.[15]

## Vascular Disease

Dysplasia of blood vessels is usually multifocal and bilateral. The most common sites are kidney and brain. Hypertension in children suggests the presence of renal artery stenosis. Usually, the aorta as well as the renal artery and its branches are dysplastic. The multifocal nature of the dysplasia with extensive involvement of the aorta often makes surgical treatment difficult.[16] Renal artery stenosis occurs in approximately 1% of patients. Dysplasia of the carotid artery and its branches is less common and results in occlusion of the carotid and proliferation of small vessels in the basal ganglia.[17]

## Neurologic Involvement in NF1

### Peripheral and Spinal Cord Involvement

Both the peripheral and central nervous system are affected in NF1. Cutaneous neurofibromas are tumors of peripheral nerves. Plexiform neurofibromas involve large nerves, plexi, spinal roots, sympathetic nerves, or small peripheral nerve fibers. Involvement of large nerves such as the sciatic may be entirely asymptomatic or suggested only by hypertrophy of the affected extremity. When the sacral plexus is involved, there can be massive proliferation of tumor with infiltration of the bladder and compression of the ureters, rectum, and uterus. Plexiform tumors of the spinal roots may cause pain and erosion of the neural foramen or cord compression. Plexiform tumors of the spinal roots occur at any level and are often found at multiple levels. High cervical cord lesions compressing the cord produce a relatively subtle syndrome with insidiously progressive ataxia, brisk deep tendon reflexes, bilateral ankle clonus, and parasthesias of the hands and feet. Involvement of the lumbar roots causes back pain that is aggravated by exertion. Dural ectasias of the spinal nerve roots may occur in the absence of any nerve root tumor at any level of the spine. Rarely, they form an anterior meningocoele.[18]

### Cognitive Problems

Learning disabilities and attention deficit occur in as many as 60% of patients. No specific learning disability is characteristic of NF1, but visual spatial difficulties are common. Attention-deficit disorder with or without hyperactivity is also frequent. Overall, intelligence in NF1 is normal. Mental retardation occurs in no more than 3%. Examination of IQ profiles suggests a bimodal curve with at least half of patients' scores distributed evenly around an IQ of 100 and another group around an IQ score of 85.[19] Unrecognized learning disabilities and attention deficit can lead to school problems and failure to achieve up to the patient's academic potential.

### Headache, Seizures, and Brain Tumors

Headaches occur in 20% of patients; most of these are consistent with migraine and respond well to prophylactic med-

ications such as amitriptyline and topiramate. Seizures, although not a prominent feature of NF1, occur in up to 10% of patients. Infantile spasms, primary generalized seizures, and partial complex seizures all occur.[20]

Brain tumors also occur with increased frequency. Brain tumors are exclusively astrocytic. Fifteen percent of patients have visual pathway/hypothalamic tumors (optic gliomas). Another 3% to 5% of patients have other types of brain tumors.[21,22] The brainstem and cerebellum are common sites for tumors, but they can also be supratentorial. Most tumors identified on magnetic resonance imaging (MRI) scan are grade I astrocytomas and do not progress. Many, if not most, are asymptomatic and do not require intervention. Biopsy should be considered only in symptomatic lesions in which there is evidence of radiologic progression. Brainstem tumors almost never progress and should be observed.[23] The majority of visual pathway tumors are also asymptomatic and static. Visual pathway tumors, however, require careful monitoring for the first 7 years of age because they can progress to compromise vision during that time period. Frequent eye examinations and MRI of the optic nerves with and without contrast are indicated in patients with change in color perception, an afferent papillary defect, optic disc pallor, or less-than-normal acuity.[24] For patients with visual pathway tumors and a demonstrable deterioration in acuity, chemotherapy should be considered. Chemotherapy stabilizes visual acuity in the majority of patients. Tumor regression or improvement in acuity is less common but occurs.[25]

Grade III and IV astrocytomas occur in NF1 and require aggressive treatment. They are invariably symptomatic. The best outcome is with complete surgical removal coupled with chemotherapy. The outcome for malignant brain tumors in patients with NF1 is generally better than the outcome in other individuals. Brain tumors need to be differentiated from asymptomatic high-intensity signal abnormalities on MRIs or unidentified bright signals. Unidentified bright signals are areas of increased signal visible primarily on T2-weighted images in the basal ganglia, thalamus, brainstem, and cerebellum. They are usually bilaterally symmetric and do not enhance with contrast. They have been suggested to be either hamartomas or proliferations of blood vessels with surrounding increased tissue edema. However, the magnetic resonance signal characteristics are not consistent with either of these possibilities. Hamartomas rarely occur in NF1 and are isolated lesions visible on T1 and T2 images, often in the frontal or temporal lobes. In addition, the bright-signal abnormalities of NF1 are not static. They are common in children but decrease in size and frequency with age.[26] They are more common in children with learning disabilities but also occur in children with no cognitive difficulties. Although they are a puzzling phenomenon, they do not require imaging to monitor their status. MRI should be reserved exclusively for patients who have symptoms suggestive of a progressive brain or optic nerve lesion. The danger of imaging to screen for tumors in asymptomatic patients is that static benign lesions are not uncommon. Once a lesion is found, the physician is obligated to monitor the lesion at intervals for an indeterminate amount of time to prove that it is indeed benign.

## Deafness, Hydrocephalus, and Stroke

Deafness, hydrocephalus, and stroke are uncommon problems in patients with NF1. Deafness, usually associated with NF2, occurs in about 10% of patients with NF1. The hearing loss is unilateral and due to a variety of causes.[27] It is noted within the first few years of life. Children who fail hearing screens or have language delay should have a careful audiology evaluation and may require brain imaging. Aqueductal stenosis occurs in 1% of patients, usually in late childhood.[28] The clinical manifestations are problems with gross motor coordination, falling, ataxia, and headache that fluctuate. The onset is insidious and often overlooked. Proliferation of tissue in the hypothalamus obstructing the aqueduct causes dilation of the lateral and third ventricles, whereas the fourth ventricle remains normal in size. It is best treated by fenestration of the third ventricle. Ventricular peritoneal shunting is also effective. Stroke occurs in less than 1% of patients. It is caused by the occlusion of the internal carotid or middle cerebral artery with proliferation of small vessels in the basal ganglia resulting in large cortical strokes. This complication usually occurs in childhood without warning. Because it appears to be a congenital abnormality, carotid Doppler screening might identify patients before stroke.

## Pain in NF1

Severe pain is an infrequent feature of NF1. Head pain, primarily migraine is common, but is usually controlled with prophylactic medication. Cutaneous neurofibromas are sometimes painful as they first emerge or when fully developed tumors are traumatized. Paraspinal plexiform neurofibromas will sometimes produce nerve root pain. Superficial plexiform tumors are painful with trauma and sometimes with compression; however, the vast majority of plexiform neurofibromas are asymptomatic. One exception is dural ectasia, which can produce intractable pain. Otherwise, when a patient with NF1 complains of significant pain, the possibility of a malignant peripheral nerve sheath tumor must be considered. These tumors are invariably heralded by the onset of severe pain.

## Malignancy

Malignancy is primarily a complication of young adults with NF1. The overall incidence of cancer is 3% more than the general population. Unusual tumors occur with increased frequency in NF1. Carcinoid, pheochromocytoma, brain tumors, chronic myeloid leukemia, and malignant peripheral nerve sheath tumors all occur. In contrast, common tumors such as breast, lung, kidney, colon, and prostate occur, but their frequency is less than in the normal population.[29]

Malignant peripheral nerve sheath tumors (MPNSTs) are a particularly devastating complication. These tumors arise from plexiform neurofibromas. The incidence is 3% of all patients with NF1. The greatest risk period is between 15 and 40 years of age. The tumors are invariably associated with severe pain. They are often multicentric with rapid hematogenous spread. Metastasis to the lungs may occur shortly after presentation. The treatment is complete surgical excision with chemotherapy, but survival beyond a year is unusual. Triton tumors are a variant of MPNSTs.[30]

**Table 2** Management of Patients with NF1

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| Parents must be examined. If a parent is affected, all of the children must be examined. Affected parents need to understand that there is a 50% risk of NF1 for each pregnancy. |
| Assessment of patients for other issues is age specific: |
| Age 0–8 years: |
| Careful physical examination looking for long bone bowing, limb asymmetry, scoliosis |
| Blood pressure check; eye examination by pediatric ophthalmologist |
| Assess developmental, language, and learning |
| Age 8–15 years: |
| Careful physical examination looking for scoliosis, limb asymmetry, neurofibromas |
| Review school performance looking for learning disabilities and attention deficit; discuss NF and the affect of puberty on NF, and ask about socialization and self-esteem |
| Age 16–21 years: |
| Careful physical examination looking for neurofibromas. Obtain imaging studies to evaluate any complaints of pain |
| Review school performance, discuss NF, and ask about socialization, and self-esteem |
| Discuss inheritance of NF1, and risk for pregnancy |
| Discuss the effects of puberty, pregnancy, and birth control pills on NF |
| Age >21 years: |
| Careful physical examination, and blood pressure check |
| Imaging studies to evaluate any complaint of pain |
| Discuss cutaneous neurofibromas, pain, and the risk of cancer |
| Discuss socialization, and career/jobs |

Imaging studies are indicated only for evaluation of specific complaints.

## Morbidity and Mortality in NF1

Stigmatizing visible cutaneous lesions, seizures, visual impairment, hearing loss, learning disabilities, stroke, spinal cord compression, pain, bowel and bladder compromise, and the psychological burden of a chronic, unpredictable, and potentially disfiguring disease all contribute to the morbidity of NF1. Fortunately, some of these complications are infrequent. Children often seem well adjusted, but psychosocial problems remain a significant concern. Mental retardation, dysmorphic facial features, and to a lesser extent early tumor burden are more common in patients with large gene deletions, but, as yet, there is no clear genotype/phenotype correlation.[31]

The life expectancy is slightly reduced. The best study of this was confounded by inclusion of patients with NF2. However, the increased incidence of unusual tumors such as MPNSTs and malignant brain tumors is consistent with an increased mortality rate in young adults. Cardiac disease may be another cause of mortality.[32]

## Management of Patients with NF1

The first step in management is genetic counseling. It is essential to examine parents to determine whether they are affected. Half of all cases are familial. It is not unusual to diagnose NF1 in a child and discover that 1 parent is mildly affected and unaware of the condition. If a parent is affected, the parents must understand there is a 50% risk of NF for each pregnancy and what that risk implies; they need to have some appreciation of the potential problems that NF1 presents (Table 2).

Regular medical appointments to a multidisciplinary clinic are also essential. In the first 10 years of life, annual examinations are recommended. Annual eye examinations by a pediatric ophthalmologist are essential until 8 years of age. The physical examination should focus on problems appropriate to the age. Because of the high incidence of learning problems, cognitive development and school performance must be carefully monitored. I emphasize early reading readiness in preschool children. If there is any suggestion of academic difficulties, a complete neuropsychological evaluation with intellectual testing is imperative. Speech problems should be aggressively addressed as early as possible with individual speech therapy. In preteens and teenagers, I ask about socialization as well as academic achievement. Teenagers need to understand the risk of NF in pregnancies. Young adults need to be seen less frequently, unless there are specific problems. Pain needs to be carefully evaluated in young adults because of the risk of MPNSTs. The potential for estrogens or oral contraceptives to increase the size or number of neurofibromas also needs to be discussed.

Imaging studies are indicated only when patients are symptomatic. There is a high incidence of asymptomatic lesions in NF1. Identification of those lesions does not help the management of patients. Moreover, if lesions are found on imaging, the physician is obligated to repeat the imaging at intervals for an indeterminate time to prove the lesions are benign. This causes unnecessary cost and anxiety.

Surgery is currently the only treatment option for most of the lesions in NF1. Chemotherapy is helpful with visual pathway tumors and grade III and IV astrocytomas. No chemotherapy has yet been identified to treat plexiform neurofibromas. Radiation therapy should be avoided except with malignant tumors because it can stimulate the growth of plexiform lesions. Surgical removal of cutaneous neurofibromas is indicated if they are causing discomfort or are visible and stigmatizing. Resection of plexiform tumors is more difficult because they frequently have diffuse projections that make complete removal impossible. Plexiform neurofibromas sometimes involve motor nerves so that resection results in disability. Nevertheless, resection of plexiform lesions

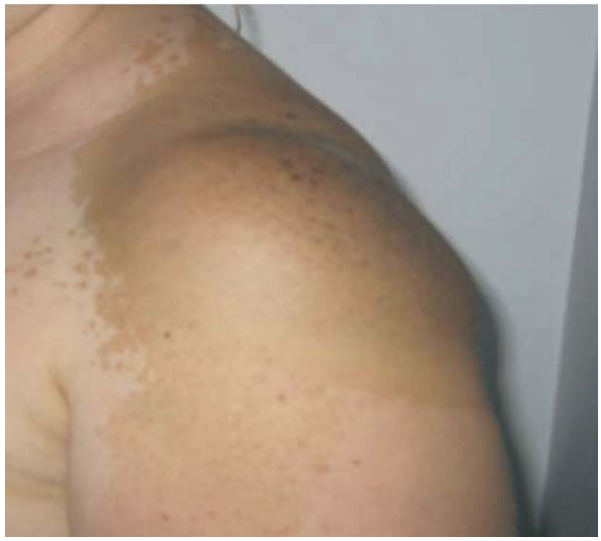

**Figure 3** Plexiform neurofibroma. This patient has a superficial plexiform neurofibromas that is raised spongy and diffusely infiltrative lesion on the shoulder associated with hyperpigmentation.

should be considered when there is cosmetic disfigurement, pain, or compromise of function. Careful imaging of tumors is essential to define the boundaries of the tumor and evaluate the vascular supply. Plexiform neurofibromas are often association with dilated veins that cause substantial blood loss.[33]

I strongly encourage physicians, patients, and parents to participate in support groups. These groups educate patients and inform them of advances in treatment and provide valuable social and emotional support. The myriad of potential complications of NF1 provides challenges throughout the lifetime of the patient. Support groups help to establish a collaborative relationship between the patient and physician that is essential.Fig 3

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